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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
1652	12

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,686	TSIEN ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *16-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,8,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-23 are pending.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-15, in Paper No.10 filed June 11, 2003 is acknowledged. The traversal is on the ground(s) that "all these claims [1-23] disclose related inventions that share a **common feature** (a modified Aequorea green fluorescent protein, provided either directly or by expression) exhibiting a **common functional property** (fluorescence)" (Remarks, page 2). This is not found persuasive because the claims drawn to a protein (independently on the method of making thereof) are not and would not have been restricted. Furthermore, the nucleic acids of Group II do not fluoresce.

The requirement is still deemed proper and is therefore made FINAL.

Claims 16-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups II-III, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Information Disclosure Statement

As part of the information disclosure statement filed December 17, 2001, Applicants provided a copy of form PTO-892 from the parent application 09/057,995. If Applicants wish for the Wood et al. reference lined through on said copy of form PTO-892 to be listed on the issued patent, they should resubmit it as typed on a form PTO-1449.

Specification

The instant disclosure contains sequence disclosure that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, there is no paper copy of the Sequence Listing in the instant application. The computer readable form (CRF) has been transferred from the parent case 09/057,995 as requested by Applicants. US PTO does not transfer paper copies. Applicants have to submit the paper copy of the Sequence Listing together with a statement that it is identical to the CRF present in the file. No CRF is required.

Further, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. 37 CFR 1.821(d) requires the use of assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences. For example, on page 18 the sequences are recited without sequence identifiers.

The specification is objected to because "GFP" is mistyped on page 1, last paragraph.

Claim Objections

Claim 1 is objected to because of the following: reference to SEQ ID NO:2 should be given in parenthesis, as is customary, not in brackets or as "having the amino acid sequence of SEQ ID NO:2.

Claim 13 is objected to because of the following typographical errors: on line 1, "m" should be deleted and on line 2 "from" should be typed correctly and space should be deleted before the period at the end of the claim.

Claim 14 is objected to because of the following: the second period should be deleted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "a modified form of an *Aequorea* wild-type GFP polypeptide" of SEQ ID NO:2 exhibiting a different excitation and/or emission spectrum from a wild type GFP. No maximum wave lengths of said peaks are defined. Claims 2, 3, 5, 8 and 13 recite qualitative limitations on the intensity of the peaks. Thus, these claims encompass a genus of molecules described by function only. The dependent claims 4, 6, 7, 9-12, 14 and 15 recite a modified form of wt GFP that comprises the specific muations. Claim 4 recites S202F/T203I. Claim 6 recites I167V/T. Claim 7 recites S65T/M153A/K238E. Claims 9 recites Y66F/H/W. Claim 10 recites Y66H/Y145F. Claims 11 recites Y66W/N146I/M153T/V163A/N212K. Claim 12 recites Y66W/I123V/Y145H/H148R/M153T/V163A/N212K. Claim 14 recites S65A/C/T/L/V/I. Claim 15 depends from claim 14 and recites S65C/T.

The specific recited mutations constitute no more than 2.9% of the entire SEQ ID NO:2 that is 238 amino acids long. The use of open language such as "comprises" results in the claims encompassing any structure as long as said structure comprises the above mutations.

The specification teaches the representative species of such modified GFPs having the amino acid sequences that differ from SEQ ID NO:2 by only the recited mutations with the rest of SEQ ID NO:2 intact. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of exhibiting a different fluorescence.

However, when, like in the instant case, there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only several species within the genus wherein the correlation between the structure and function (fluorescent characteristics) is neither known in the art nor disclosed by the specification.

Thus, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified GFP comprising the amino acid sequence that differs from SEQ ID NO:2 by only mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I, does not

reasonably provide enablement for a modified *Aequorea* GFP having the amino acid sequence of SEQ ID NO: 2 comprisng mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-15 recite a modified *Aequorea* GFP comprising the amino acid sequence set forth in SEQ ID NO:2 comprising mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I. This amounts to

a modified GFP having any structure as long as its structure comprises the above mutations.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any GFP sequence that comprises mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting the specific requisite activity of the polypeptide of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Despite knowledge in the art to produce mutations in proteins, the specification fails to provide guidance as to where, and what type of (i.e., what amino acid to substitute into, add to or delete from the known sequence), changes in amino acid residues will result in a desired biological activity. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in a certain activity is

extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited.

Furthermore, while recombinant and mutagenesis techniques are known, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure.

Therefore, one of ordinary skill in the art would require guidance, beyond that provided, in order to make a modified GFP having an amino acid sequence of an unknown homology to SEQ ID NO:2 comprising mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, with dependent claims 2-15, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a fluorescent product derived from a modified form of an *Aequorea* wild-type GFP polypeptide. The metes and bonds of the term "derived" are defined neither in the specification nor the art rendering the claim unclear.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-64 of U.S. Patent No. 5,777,079 (form PTO-1449, reference P11, filed December 17, 2001). Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass or recite a fluorescent protein or a fusion protein comprising thereof when said fluorescent protein comprises the same mutations in *Aequorea* GFP as recited in instant claims 1-15. Further, it would have been obvious to one of ordinary skill in the art to make a fluorescent product such as a fusion protein comprising modified GFP as taught by inventors (column 1, lines 18-31, for example). A solution of a fusion protein, for example, represents a composition of matter.

Claims 1-3 and 8-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,066,476. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of US 6,066,476 is drawn to a mutant fluorescent protein comprising a substitution at position 65. Claims 2-5 are drawn to a fusion protein comprising a substitution at position 65 or at position 66. It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a fluorescent product such as fusion protein comprising modified GFP as

taught by inventors (column 1, lines 18-31, for example). A solution of a fusion protein represents a composition of matter.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Claims 1 and 16 of US 6,140,132 are drawn to a functional engineered fluorescent protein having the amino acid sequence that differs from SEQ ID NO:2 by mutations K26R/F64L/**S65T/Y66W**/N146I/M153T/V163A/N164H/H231I and to a kit comprising thereof, respectively (emphasis added). US 6,140,132 was filed on June 9, 1998 after the effective filing date of the instant application of November 10, 1994. Therefore, the two way test for ODP-obviousness test is not met.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
August 15, 2003